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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,204	07/10/2006	Stanislaw Joseph Urbaniak	ABLE0032US.NP	6475

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
07/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/563,204	URBANIAK ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 11-17* is/are pending in the application.

4a) Of the above claim(s) *1-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A petition to revive the instant application was granted by Shirene Willis Brantley on January 14, 2009. As such, applicant's response to the restriction requirement received December 12, 2008 as part of the aforementioned petition has been entered.

Claims 1-7 and 11-17 are pending in the instant application.

2. Applicant's election with traverse of the invention of Group II, claims 11-17, drawn to methods of administration in the reply filed on December 12, 2008 is acknowledged. The traversal is on the ground(s) that the GPIIIa peptides of the prior art are disclosed as working in a manner different to how applicant believes the instant invention works. Specifically, applicant argues about how the prior art peptides comprise conformational epitopes bound by antibodies whereas the asserted invention is linear epitopes that bind T cells. This is not found persuasive because applicant has argued limitations not claimed. The recited products are not limited in size to short peptides of an exactly defined sequence. Thus the longer peptides of Bowditch et al. comprise the linear epitopes argued by applicant. Further, the peptide compositions of Bowditch et al. are disclosed as being in oral and suppository form, both of which are formulations for delivery via non-invasive routes. Thus there is no structure recited in the instant product claims that is not disclosed by Bowditch et al. As such, the technical feature of the instant invention (the polypeptides that are administered) are not distinct from the structure of the polypeptides of the prior art and therefore applicant's argument that the instant claimed inventions are entitled to unity of invention is not persuasive.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

3. The IDS submitted 2/8/06 is acknowledged.

Specification

4. The title and abstract are both objected to for not specifying the instant claimed subject material. Specifically, neither discloses methods of administration. Appropriate amendment is suggested.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 11, 12, and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has filed broad claims for the prevention and management of conditions caused by exposure to an allogeneic platelet protein which comprise administration of an allogeneic platelet protein to a patient. The specification discuses at length human platelet antigen (HPA) which is actually alleles of human GPIIIa which are present in the out-bred human population and differ from one another by singe amino acid substitutions as is detailed on page 6 of the instant specification. The claims are not limited to GPIIIa, but encompass allotypic variations at any and all proteins that are present in platelets, as well as all possible fragments of said platelet proteins. While the specification does indicate that mismatched alleles of GPIIIa between an mother and her baby can cause FMAIT, and that mismatched GPIIIa alleles between a platelet donor and recipient can cause post-transfusion purpura and platelet refractoriness, there is no disclosure of other disorders or conditions which may arise from mismatched GPIIIa alleles, or that mismatched alleles of platelet proteins other than GPIIIa lead to clinically observed conditions and disorders.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As discussed above, applicant has not established that differing alleles of platelet proteins excepting GPIIIa lead to observable clinical conditions, or that mismatches of

GPIIIa lead to conditions other than those recited in claim 12. Further, the species of GPIIIa as a platelet protein is not representative of the breadth of the genus of all possible platelet polypeptides and fragments thereof because the genus of all platelet proteins encompasses structurally and functionally unrelated proteins. As such guidance and direction as to what the alleles of GPIIIa are provides no insight into what alleles may or may not be present for a different platelet protein nor does information concerning GPIIIa allow for prediction as to how the alleles of a different protein differ from one another. For example, GPIIIa alleles appear to be single point mutations, but other alleles of other proteins may comprise unique exons, inversions, deletions, multiple substitutions, and combinations thereof. Therefore, a skilled artisan would not reasonably believe that applicant was in possession of all possible allelic variants of all platelet proteins at the time the instant invention was filed and therefore a skilled artisan would reasonably conclude that applicant was not in possession of the breadth of the claimed methods of use of such proteins at the time the instant invention was filed.

7. Claims 11-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has claimed generic methods of preventing and managing conditions resulting from exposure to allogeneic platelet proteins, with dependent claims limiting the platelet protein to human platelet antigen (HPA) which is also known as glycoprotein IIIa (GPIIIa). The specification discloses that 15 mer peptides which are subsequences of GPIIIa which comprise the substitution of leucine for proline at position 33 of the full length sequence, when presented by appropriate MHC matched APC can be used to stimulate T cells in PBMC isolated from mothers who developed anti-GPIIIa alloantibodies as a result of a pregnancy. The specification asserts that

immunodominant T cell epitopes of GPIIIa identified by applicants can be used to induce tolerance to allogeneic GPIIIa proteins on page 15, but no data or working examples concerning the administration of such peptides to patients, human or otherwise, is presented in the specification. It should also be noted that while the instant claims do not specifically recite administering to a human patient, it is clear from the text of the specification, the fact that the sequences recited in the dependent claims are human GPIIIa sequences, and the general disinterest in the art for treating conditions such as FMAIT, post-transfusion purpura, and platelet refractoriness in non-human subjects, that the purpose of applicant's claimed invention clearly is the treatment of human patients, and the claims have been examined in this light.

However, the specification's disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding *in vivo* methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)."

Attempts to induce tolerance in humans have been completely unsuccessful in multiple different documented instances. See for example, *Marketletter* (9/13/99) which teaches the complete failure of tolerance induction in human trials. Both Myloral (for multiple sclerosis, MS) and Colloral (for rheumatoid arthritis, RA) provided successful results in inducing tolerance in small in-bred animal models, however, both were complete failures in human trials. Also see Pozzilli et al. (2000), wherein the authors demonstrate that, while the induction of tolerance to orally administered insulin for the treatment of diabetes might have been expected, it simply did not occur. The authors could only speculate as to the reasons for the trial's failure. The authors did note one complicating factor that has been reported several times, and will have to be considered in all future work, a large placebo effect wherein both the treated and control subjects showed similar temporary improvement. Three years later Skyler et al. (2005) reported another failure in one of the largest placebo-controlled tolerance trials ever performed in humans (the administration of insulin for the prevention of type 1 diabetes).

Other investigators have gone beyond simply reporting and have tried to consider the reasons for the unexplained problems in establishing human tolerance. See, for example, Dong et al. (1999):

> "Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. *Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn*", (emphasis added).

WO 02/053092 teaches that the oral administration of antigens for the induction of tolerance presents numerous additional "obstacles", including the problem of accurate dosing given the necessity of digestion which alters both concentration and structure of the antigens. In that work the inventors conclude that:

> "oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even *in vitro* results, and must result from extensive empirical experimentation" (page 23)

In another attempt to explain these repeated failures Goodnow (2001) states:

> "Obtaining the desired response [tolerance] with these strategies [tolerance induction] is unpredictable because many of these signals [tolerogenic] have both tolerogenic and immunogenic roles"

(see the Abstract). The author goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in humans because of the lack of understanding of the mechanisms involved (page 2120, column 2). Note that an oral medication would be absorbed by the gastrointestinal mucosa.

More recently, Kraus and Mayer (2005) looked at tolerance induction in inflammatory bowel disease (IBD). They reported the ease with which tolerance is induced in in-bred experimental mice and contrasted that with the difficulty in inducing tolerance in humans. Speculating on the reasons for the difference the authors considered a lack of dosing optimization but went on to report that *the mechanisms of tolerance induction in humans and mice appear to be fundamentally different*. Most importantly, Kraus and Mayer report a genetic component wherein many IBD patients and their family members appear to be *incapable* of becoming tolerant to oral antigens because they lack the ability to generate the required T regulatory cells. If confirmed, this would mean that *no* tolerance induction regime could work in these patients.

Even more recent work has attempted to duplicate favorable results established in in-bred animal models in a more complex mouse model more realistic to the out-bred human population. See, for example, Bell et al. (2008). The authors employed F_1 hybrid mice (a cross between two in-bred strains) wherein they asked if toleragens that worked in the parent strains would induce tolerance in the crossed F_1 hybrid mice. Unfortunately the results showed that in one instance not only was tolerance not induced, but disease was actually exacerbated. Thus, the work serves as a clear demonstration that the induction of immune tolerance is far from predictable in anything other than carefully chosen in-bred experimental mouse strains.

As set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art, "would accept without question" an Applicant's statements regarding an invention,

particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

A review of the instant specification shows no induction of tolerance.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Given that the induction of immune tolerance has been referred to as the seeking of the "Holy Grail" of transplantation (Schroeder et al. (2003)), fraught with difficulties not even considered in the instant specification, further in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses no data relevant to the induction of tolerance, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 11-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims16-22 of copending Application No. 12/096,092. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims also recite methods of administering peptides to cause tolerization in a patient exposed to an antithetical allele. The copending methods recite that the tolerizing peptide is a T cell antigen and that the treated disorders include transfusion reactions. Thus the copending claims anticipate some of the instant claims and significantly overlap in scope with other claims of the instant invention. .

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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